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Research Progress on Comorbid Depression in Epilepsy

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Abstract

Comorbid depression in epilepsy is a prevalent and severe clinical condition that significantly increases the psychosocial burden of patients. In recent years, with advances in research on its pathological mechanisms, the core biological processes underlying comorbid depression in epilepsy have become increasingly clarified. Its pathogenesis involves multiple pathways, including neurotransmitter imbalance, inflammation, genetic variations, and neuroendocrine abnormalities. This review summarizes the core pathological mechanisms of comorbid depression in epilepsy from four perspectives: neurotransmission, neuroendocrinology, hippocampal structure, and neuroinflammation, aiming to provide theoretical support for clinical diagnosis and treatment.

Keywords: Epilepsy; Depression; Comorbidity; Pathogenesis

1. Introduction

The prevalence of depression is rising year by year, and comorbid depression in patients with somatic diseases has attracted increasing attention in both clinical practice and scientific research. Among common neurological comorbidities, depression comorbid with epilepsy has become a major research focus owing to its high prevalence and severe clinical impacts. Comorbid depression not only worsens the frequency and severity of epileptic seizures but also significantly increases the risk of sudden unexpected death in epilepsy (SUDEP). The pathogenesis of depression comorbid with epilepsy is complex and heterogeneous, and exploring its key regulatory nodes and core pathways is of great research significance. Therefore, a systematic review of its pathophysiological mechanisms is clinically critical for the early identification, precise intervention, and optimized management of this comorbidity.

2. Monoamine Neurotransmitter Mechanisms

Monoamine neurotransmitter dysfunction erves as a key mechanism underlying epilepsy comorbid depression, which is accompanied by overlapping structural and functional alterations in the central nervous system. The primary neurotransmitters involved incude 5-hydroxytryptamine (5-HT), norepinephrine (NE), and dopamine (DA).

2.1. Serotonin System

5-HT is widely distributed in the raphe nuclei, prefrontal cortex, and hippocampus, where it modulates emotion, behavior, and epileptogenesis. In depression, downregulation of the 5-hydroxytryptamine 2A receptor (5-HT_2A receptor) in the medial prefrontal cortex induces excessive glutamate (Glu) release, impaired synaptic plasticity, neuronal dysfunction, and depression-like behaviors (González-Arias et al., 2023). Such excessive Glu disrupts the excitation/inhibition balance and increases seizure susceptibility. Notably, reduced 5-HT levels and metabolism are observed in both depression and epilepsy. Using the 5-HT_2A agonist Cimbi 36, Erritzoe et al. (2023) directly measured brain 5-HT release in 17 depressed patients and 20 healthy controls, demonstrating reduced 5-HT levels and confirming 5-HT dysfunction as a core feature of depression. Consistently, impaired central 5-HT signaling is closely associated with epileptic activity, identifying the central 5-HT system as a key hub in epilepsy–depression comorbidity.

In temporal lobe epilepsy (TLE) models, reduced extracellular 5-HT is a hallmark of comorbid depression. 5-HT depletion reduces 5-hydroxytryptamine 1A receptor (5-HT_1A receptor) binding potential, whereas increasing 5-HT signaling exerts seizure-inhibitory effects (Bølling-Ladegaard et al., 2023). Recurrent seizures induce neuronal damage, impair 5-HT metabolism, and thereby promote depressive symptoms (Schönhoff et al., 2021). 5-HT deficiency appears critical in this comorbidity, as the severity of comorbid depression correlates negatively with serum 5-HT concentrations (Sun et al., 2024). Furthermore, lacosamide exerts both antiepileptic and antidepressant effects by elevating 5-HT levels and reducing Interleukin-6 (IL-6) expression (Li et al., 2025), supporting the 5-HT system as a critical mechanistic link between epilepsy and depression.

2.2. Norepinephrine System

Dysfunction of the NE system is closely associated with the occurrence and progression of epilepsy and depression. NE not only directly modulates epileptic seizures but is also closely linked to SUDEP. NE and 5-HT neurons participate in the regulation of SUDEP through synergistic effects, with the dorsal raphe nucleus (DR)–locus coeruleus –parabrachial nucleus (PBN) circuit serving as the key neural pathway. This pathway can inhibit seizure-induced respiratory arrest associated with epileptic seizures by activating 5-HT_2A receptors and NE-α_1 receptors in the PBN, thereby reducing the risk of SUDEP (Xu et al., 2025). Under stress, the lateral habenula–locus coeruleus circuit forms a positive feedback loop that drives persistent neural hyperactivity and depression-like behaviors (Xin et al., 2024). In focal epilepsy models, the emergence of depressive-like behaviors is associated with reduced NE levels (Kumar et al., 2016). Region-specific NE regulation follows a ‘compensation-injury’ pattern: increased NE in

the locus coeruleus–cortex pathway acts as an acute adaptive antiepileptic response, whereas decreased hippocampal NE promotes neuroinflammation and epileptogenesis (Gu et al., 2025). NE also exerts antiepileptic effects by modulating free fatty acid release, linking peripheral metabolic status to central neuronal excitability (Li et al., 2025).

2.3. Dopamine System

Dopaminergic circuits regulate emotional processing, reward function, and neuronal excitability. Dopamine receptors are divided into two major families. D1-like receptors (D1LR) generally promote seizures, whereas D2-like receptors (D2LR) exert antiepileptic effects (Bozzi & Borrelli, 2013). In genetic generalized epilepsy, upregulated D1LR and downregulated D2LR in the prefrontal cortex enhance seizure susceptibility (Birioukova et al., 2024). Optogenetic manipulation of dorsal striatal neurons bidirectionally modulates epileptic seizures. Specifically, D2LR activation inhibits thalamocortical synchronous discharges, suppressing seizure motor manifestations and duration without altering the onset of epileptiform discharges (Hyder et al., 2025).

Dopaminergic imbalance contributes to epileptogenesis and mediates depressive symptoms in individuals with epilepsy. Chronic unpredictable stress suppresses DR neuronal activity and disrupts synaptic input to DA neurons; DR-DA projections to dorsal striatal $CaMKII^{++}$ neurons modulate depression-related behaviors (Wang et al., 2024). Similarly, chronic stress impairs dopaminergic transmission, whereas nucleus accumbens stimulation alleviates depressive behaviors by enhancing DA release (Song et al., 2024). In epileptic rats, DA system abnormalities are concentrated in the medial prefrontal cortex (Birioukova et al., 2024), a major target of ventral tegmental area (VTA) DA neurons (Gunaydin et al., 2014), suggesting a shared neural circuit basis for epilepsy and depression. The DA system may therefore serve as a key molecular bridge between the two disorders, informing mechanistic studies of their comorbidity.

The nigrostriatal DA pathway regulates the duration of absence seizures; its degeneration reduces DA levels and triggers compensatory increases in 5-HT, thereby prolonging spike-wave discharges (Tugba et al., 2022). This links DA dynamics to seizure activity and electroencephalography (EEG) alterations, offering potential biomarkers for comorbid disease. The serotonergic raphe nucleus–prefrontal cortex pathway and dopaminergic VTA–nucleus accumbens pathway display functional vulnerability prior to seizure onset. Chronic epilepsy progressively impairs these pathways, reducing neurotransmitter release and contributing to the development of comorbid depression (Medel-Matus et al., 2017).

D2LR agonists exert antiepileptic effects by activating parvalbumin-positive interneurons (Brodovskaya & Kapur, 2021). Although DA signaling is clearly involved in the pathogenesis of epilepsy-comorbid depression, related pharmacotherapeutic and mechanistic studies remain limited, warranting further preclinical and clinical investigations for targeted therapeutic development.

3. Hypothalamic-Pituitary-Adrenal Axis

The Hypothalamic-Pituitary-Adrena (HPA) axis connects neuroinflammation and the endocrine system, integrating neural, endocrine, and immune signals. Both epilepsy and depression disrupt HPA axis function via cytokines, and HPA hyperactivation further promotes inflammatory mediator release, forming a vicious cycle.

Overactivation of the HPA axis impairs temporal lobe structure and function, and epileptic seizures further exacerbate this injury, thereby weakening the HPA axis's normal negative feedback regulation (Basu et al., 2022; Gulyaeva, 2021) . As unpredictable stressors, epileptic seizures activate microglia to secrete inflammatory mediators including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6),which modulate HPA axis activity (Pereira et al., 2022) and contribute to the development of depressive symptoms.

Glucocorticoids (GC), the core effector molecules of HPA axis stress responses, alter hippocampal network function and related mood, learning, and memory processes when present in excess (Joëls, 2001). Recurrent seizures induce hippocampal neural network abnormalities, neuronal loss, glial proliferation, and synaptic remodeling (Choy et al., 2022), which increases neuronal spontaneous electrical activity—suggesting GC may participate in epilepsy-depression comorbidity by disrupting hippocampal structure and function. GC exert effects via the glucocorticoid receptors (GR) and mineralocorticoid receptors (MR); a central imbalance in the GR/MR ratio is key to HPA axis dysfunction and susceptibility to mental diseases (Harris et al., 2013). FK506 binding protein 5 regulates the GR pathway, with reduced expression enhancing HPA axis negative feedback (Lin et al., 2021). Meanwhile, the GR antagonist mifepristone shows promise for treating major depressive disorder (MDD) in patients with childhood trauma (Linsen et al., 2023).Hippocampal MR maintains HPA axis inhibition under basal low cortisol levels, and collaborates with GR in negative feedback regulation under stress-induced high cortisol conditions (De Kloet, 2022) . Using an in vivo dual-color reporter system, Han (Han et al., 2021)et al. first demonstrated that hippocampal GR inhibition of nuclear factor-κB (NF-κ, a key inflammatory transcription factor) occurs in three temporal phases, with late GR inactivation serving as a key switch for the transition from inflammation to depression—highlighting GR and MR as core mechanisms underlying comorbidity.

Clinical studies show that MDD patients with elevated adrenocorticotropic hormone (ACTH) levels have increased Glu and glutamine and decreased glutathione (GSH, a key antioxidant) and γ-aminobutyric acid (GABA, the major inhibitory neurotransmitter) in the dorsal anterior cingulate cortex; Notably, GSH and GABA independently predict depression severity, indicating HPA axis hyperactivity contributes to depression and cognitive impairment via an excitation-antioxidant imbalance (Tian et al., 2024). Additionally, ACTH treatment transiently reduces levels of inflammatory factors (IL-6, interferon-gamma, monocyte chemoattractant protein-1) in infants with drug-resistant epilepsy (Kaczorowska et al., 2023), indicating that ACTH may regulate seizures through immune-inflammatory modulation-neuroinflammation, epilepsy, and depression.

4. Hippocampus

As a component of the limbic system located in the medial temporal lobe, the hippocampus—comprising the hippocampus proper, dentate gyrus, subiculum, entorhinal cortex, and hippocampal remnant—regulates memory, spatial orientation, emotion, and visceral activities. Hippocampal sclerosis (HS), the most common pathological feature in TLE, is associated with a 34.5% prevalence of comorbid depression in TLE-HS patients(Visoná De Figueiredo et al., 2021).Elevated serum IL-6 and morning cortisol levels are independent risk factors for comorbid depression in TLE-HS patients (Aljafen et al., 2024). A meta-analysis reported that HS increases depression risk by 58% , with an overall prevalence 42% (Cai et al., 2023), confirming hippocampal structural abnormalities elevate epilepsy-depression comorbidity risk.

The hippocampus has CA1-CA4 subregions. Among them, CA1-CA3 are closely linke to epilepsy and depression, while CA4-related studies are limited. CA1 chandelier cells inhibit abnormal neuronal discharge via GABAergic synapses during seizures (anti-epileptic effect), and blocking their transmission exacerbates seizures (Li et al., 2026). Post-status epilepticus (SE), CA1 upregulates inflammation- and excitability-related genes, promoting epileptogenesis (Galvis-Montes et al., 2023).Psychological stress increases formaldehyde, damaging CA1 neurons, inducing apoptosis, inactivating 5-HT/DA systems, and triggering depressive-like behaviors (Wu et al., 2026). Chronic stress can downregulate the expression of Dickkopf-related protein 3 in hippocampal CA1 neurons, enhancing microglial phagocytosis of excitatory synapses and inducing depression/anxiety-like behaviors (Chen et al., 2025).CA2 neurons modulate hippocampal network excitability, and their dysfunction is associated with psychiatric disorders. In a pilocarpine-induced TLE model, CA2 pyramidal neurons show hyperexcitability and hypoinhibition; chemogenetic silencing reduces chronic seizures by 42% (Whitebirch et al., 2022), and early silencing shortens SE, improves EEG abnormalities and social behaviors (Lisgaras et al., 2023). Deletion of Efhd2-related factor 3B in the CA2 region leads to social cognitive deficits and reduced neuronal excitability (Chen et al., 2025), indicating it is a key comorbidity regulatory target. In the SE model, the complement component 3–complement component 3a receptor pathway mediates microglia-astrocyte crosstalk in CA3, participating in epilepsy-related neurodegeneration (Wei et al., 2021). Mecamylamine inhibits CA3 epileptiform discharges (Zapukhliak et al., 2021), and CA3-expressed TGR5 regulates depressive-like behaviors (Li et al., 2024). Collectively, these findings indicates that hippocampal subregional abnormalities constitute a key mechanism underlying epilepsy-depression comorbidity.

Hippocampal neuroplasticity, which refers to adaptive structural and functional changes, underpins learning, memory, and cognition. It modulates neuronal proliferation, differentiation, and synaptogenesis mainly through the Wnt/β-catenin and brain-derived neurotrophic factor (BDNF)–tropomyosin receptor kinase B (TrkB) pathways. In mouse models, cystine-rich intestinal protein-like protein 5 deficiency in glutamatergic neurons results in elevated hippocampal BDNF expression and enhanced activation of its receptor TrkB, thereby mediating spontaneous seizures (Zhu et al., 2023). BDNF-TrkB also maintains SE neuronal excitability via GluN2B-containing N-methyl-D-aspartate (I) receptors (De Luca et al., 2025). BDNF participates in epileptic memory consolidation (Lai et al., 2024), and exogenous irisin increases

BDNF, reducing seizures and neuronal damages (Yu et al., 2022). BDNF interacts with 5-HT and the HPA axis: activation of hippocampal 5-HT_1A receptors, which is regulated by GC, elicits an antidepressant effect (Wang et al., 2025). Chronic corticosterone drives dentate gyrus hyperactive autophagy, degrading BDNF and inducing depressive-like behaviors, reversible by neuron-specific autophagy-related gene 5 knockout (Zhang et al., 2023).

BDNF and 5-HT synergistically regulate comorbidity: BDNF upregulation in 5 -HT neurons activates hippocampal TrkB, improves 5-HT signaling, and enhances stress resilience, forming a BDNF–TrkB–5-HT–HPA axis regulatory mechanism that links the hippocampus, monoamines, and endocrine system (Leschik et al., 2022).

5. Cytokines and Neuroinflammation

Neuroinflammation is a key process in both epilepsy and depression. Chronic inflammation contributes to depressive behaviors through glial activation, inflammatory mediator release, and disrupted neurotransmitter metabolism. Microglia play a central role: seizures activate microglia to release proinflammatory cytokines, destabilize neural networks (Prinz et al., 2019), and increase seizure susceptibility. Stress-induced glial activation in the lateral habenula promotes depressive-like behaviors (Xin et al., 2024).

5.1. IL-6

IL-6 is a pivotal proinflammatory factor linking epilepsy and depression, and a risk factor for adult epilepsy recurrence, with its levels negatively correlated with the time to recurrence (Fang et al., 2024). In a chronic TLE rat model, hippocampal upregulation of IL-6 induces indoleamine 2,3-dioxygenase 1 expression, which increases the kynurenine/tryptophan ratio while reduces the 5-HT/tryptophan ratio, thereby triggering epilepsy-related depressive-like behaviors (De Luca et al., 2025). Additionally, a Mendelian randomization study further indicated a causal relationship between IL-6 receptor (IL-6R) antagonist and reduced epilepsy risk, underscoring that IL-6 exerts a dual regulatory effect on epilepsy and its concomitant neuropsychiatric disorders (Yu et al., 2024).

In a mouse depression model induced by chronic social defeat stress (CSDS), microglial activation elevates IL-6, promoting astrocyte apoptosis and atrophy in the hippocampal CA1, ultimately resulting in dendritic spine loss and depressive-like behaviors (Shen et al., 2025). Notably, knockdown of the IL-6R significantly reduces its expression in astrocytes and effectively reverses CSDS-induced astrocyte atrophy, as reflected by a marked increase in cellular branch numbers. Furthermore, Lactobacillus reuteri L6 alleviates depressive-like behaviors by inhibiting IL-6 expression, upregulating BDNF and 5-HT levels, and enhancing GABAergic signaling (Ma et al., 2024), which provides a novel approach for intervening in epilepsy comorbid with depression through intestinal flora regulation.

5.2. TNF-α

Elevated TNF-α levels are closely and significantly associated with depressive symptoms, further supporting the "inflammation-depression" causal pathway (Martino et al., 2025).

Specifically, increased peripheral TNF-α elevates the central self-stimulation threshold in mice, reduces reward sensitivity and induces anhedonia—a core clinical symptom of depression (Van Heesch et al., 2013). Peripheral TNF-α levels are significantly elevated within 24 hours after epileptic seizures, which promotes Glu release, impairs GABAergic inhibitory function, and further disrupts the excitation-inhibition balance of neurons (Han et al., 2018). Excessive TNF-α signaling can further exaggerate Glu release and suppress GABAergic transmission, thereby exacerbating subsequent epileptic seizures and neuronal injury (Han et al., 2018). Accumulating evidence has demonstrated that decreasing TNF-α levels, inhibiting NF-κB pathway activation, and restoring hippocampal 5-HT levels effectively ameliorate depressive- like behaviors (Tarwani et al., 2025). These findings collectively provide a potential novel therapeutic target for the management of epilepsy comorbid with depression.

5.3. IL-1β

Elevated plasma IL-1β levels are specifically associated with epilepsy-related depression (Vieira et al., 2015). As a critical proinflammatory cytokine, IL-1β exerts dual pathogenic effects by disrupting neuronal function and triggering neuroinflammatory responses, which collectively contribute to the progression of both epilepsy and depression.

Specifically, IL-1β promotes Glu release and inhibits GABA function, which disrupts the balance between excitatory and inhibitory neurons, enhances neuronal hyperexcitability, and thereby increases seizure susceptibility. Concurrently, IL-1β induces the activation of the NF-κB pathway in microglia, which in turn upregulates the production of nitric oxide (NO) (Ferreira et al., 2010). Notably, NO exerts a concentration-dependent effect on neuronal function: low concentraions exert neuroprotective effects, whereas high concentrations inhibit the activity of neuronal mitochondrial cytochrome oxidase, leading to neuronal depolarization and further promoting Glu release (Bal-Price & Brown, 2001). Abnormally elevated levels of Glu and NO then overactivate NMDA receptors, ultimately inducing abnormal neuronal discharge and exacerbating both epileptic seizures and neural damage. Beyond its effects on epileptogenesis, excessive IL-1β contributes to depressive phenotypes through multiple pathways. It induces intracellular calcium overload in neurons, which further aggravates neuronal apoptosis and brain injury. Moreover, IL-1β can cross the blood-brain barrier to activate the HPA axis, promoting the overproduction of cortisol; this excessive cortisol release not only exacerbates neuroinflammation (Sălcudean et al., 2025) but also disrupts the balance of neurotransmitters closely associated with depression, including 5-HT and DA (Kim et al., 2016).

Furthermore, accumulating evidence highlights the link between IL-1β and cognitive as well as emotional dysregulation in depression. Serum IL-1β levels are positively correlated with the severity of cognitive impairment in patients with depression (Jin et al., 2020). In addition, IL-1β serves as a critical regulator of pathways that modulate abnormal functional connectivity between the middle frontal gyrus and mid-anterior cingulate cortex/insula, which in turn exacerbate depressive symptoms in patients with bipolar II depression (Xiao et al., 2024).

Collectively, these findings indicate that IL-1β acts as a central mediator in the “inflammation-brain network-emotion” axis, providing a novel IL-1β-targeted therapeutic strategy for the

tripartite intervention of epilepsy, depression, and their comorbidity.

6. Conclusion

The pathophysiological mechanism of comorbid depression in epilepsy involves a synergistic effect of multiple pathways, including NE dysregulation, abnormal signaling between 5-HT neurons and astrocytes, and neuroinflammation. The interactive relationships and final effects of these pathways are shown in the mechanism diagram (Figure 1). Elucidating these mechanisms supports early screening, targeted therapy, and prognostic evaluation. However, most current studies focus on single mechanisms rather than integrated networks, and core drivers remain unclear. Additionally, evidence is largely derived from animal and basic research, with insufficient high-quality clinical cohort and longitudinal studies. Therefore, further translational research is needed to characterize the human pathophysiology of epilepsy-comorbid depression.

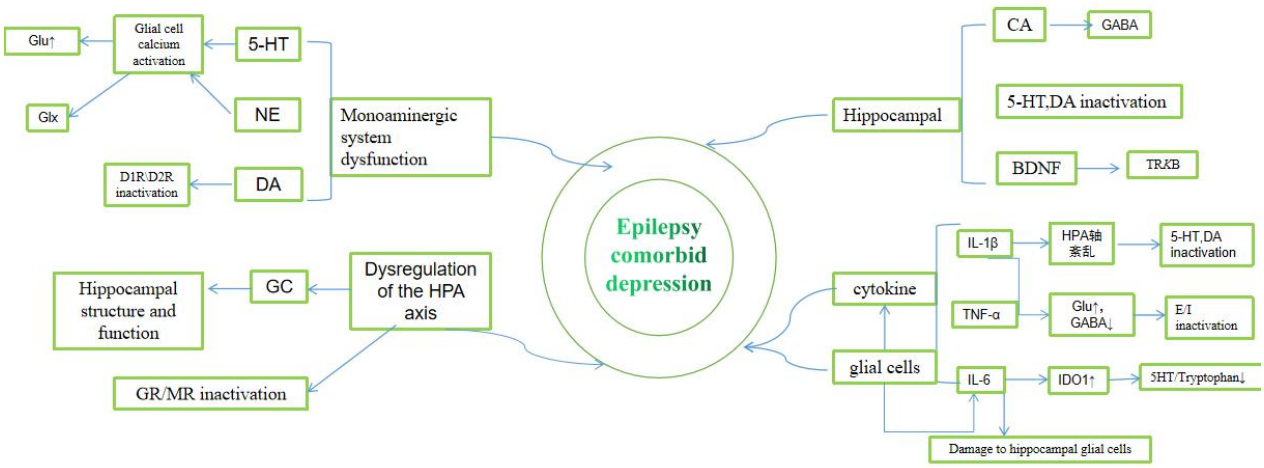

Figure 1. The mechanism diagram

Appendix:

Appendix1. List of abbreviations

English abbreviation	Full name
SUDEP	Sudden unexpected death in epilepsy
5- HT	5- hydroxytryptamine
NE	Norepinephrine
DA	Dopamine
5-HT_2A receptor	The 5-hydroxytryptamine 2A receptor
Glu	Glutamate

TLE	Temporal lobe epilepsy
5-HT$_1$A receptor	5-hydroxytryptamine 1A receptor
DR	Dorsal raphe
PBN	parabrachial nucleus
D1LR	D1- like receptors
D2LR	D2- like receptors
VTA	Ventral tegmental area
EEG	Electroencephalography
HPA	Hypothalamic-pituitary-adrenal
IL-1β	Interleukin-1β
TNF-α	Tumor necrosis factor-α
IL-6	Interleukin-6
GC	Glucocorticoids
GR	Glucocorticoid receptors
MR	Mineralocorticoid receptors
MDD	Major depressive disorder
NF-κB	Nuclear factor-κB
ACTH	Adrenocorticotropic hormone
GABA	γ-aminobutyric acid
HS	Hippocampal sclerosis
SE	Status epilepticus
BDNF	Brain-derived neurotrophic factor
TrkB	Ttropomyosin receptor kinase B
NMDA	N- methyl- D- aspartate
IL-6R	IL-6 receptor
CSDS	Chronic social defeat stress
NO	Nitric oxide

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